Improving Chemical Risk Assessment with Better Exposure Assessments

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Agency Problem/Client Need: Risk assessors within and outside the Agency need guidance on how to conduct exposure assessments. They need statistically based exposure factors (e.g., food consumption rates, children's soil ingestion rates, dermal exposure factors) in order to craft defensible scenarios and produce reliable estimates of dose. They also need chemical-specific exposure information, as most Agency programs regulate on a chemical-specific basis. Dermal contact with environmental contaminants is possible at virtually all exposure sites, and it is important to be able to demonstrate, in a scientifically defensible manner, its contribution to human health risk.

Science Questions: Exposure factors research attempts to answer questions such as: What is the interindividual variability in exposure factors; and Are certain members of the population more highly exposed than the general population? The chemical assessments address questions such as: What are the sources, releases, levels in various media, and exposure pathways? Dermal exposure research seeks to answer the question, what is best way to estimate dermal absorption resulting from contact with chemically contaminated soil, water, or sediment?

Approach: The exposure program addresses three areas: exposure factors, chemical assessments, and methods development, which is currently focused on dermal assessments. Literature searches and critical reviews are used to compile information and data. Uncertainties and data gaps are identified and field studies are often used to fill such gaps. Models are used to evaluate fate and transport, estimate exposures/doses, and predict body burdens. These efforts are conducted both in-house and with extramural vehicles. Collaborations with other ORD laboratories, research institutions, and Program Offices are also important. For example, data generated by the National Exposure Research Laboratory (NERL) is incorporated into the *Exposure Factors Handbook* and the *Child-Specific Exposure Factors Handbook.* Likewise, data from the handbooks are used by ORD scientists as input to exposure models (i.e., Simulation of Human Exposure and Dose System [SHEDS]). An NCEA-led intra-Agency Exposure Factors Program Advisory Group helps identify research areas of high priority to the Program Offices.

Results/Outcomes: The major products of the factors program are the *Exposure Factors Handbook* and the *Child-Specific Exposure Factors Handbook*. Over the past 5 years, NCEA has produced 50 chemical exposure summaries as well as detailed exposure chapters (on 1,1,2-trichloroethane [TCE], formaldehyde, and antimony) for Integrated Risk Information System (IRIS) Program assessments. A special project on polybrominated diphenyl ethers (PBDE) has produced a journal article and an EPA Report is currently being drafted. The chemical-specific program has had the lead on developing the exposure portion of the Dioxin Reassessment since its inception. The dermal program has compared and evaluated dermal assessment methods across Agency programs (in collaboration with the Risk Assessment Forum [RAF]) and completed projects on sediment adherence, methods for testing lipophilics, in vitro methods, and absorption from soils.

Impacts: The Handbooks are used extensively within and outside of EPA and have helped standardize Agency exposure assessments. NCEA's chemical exposure assessments have supported numerous health assessments and contributed to the development of assessment methods. The soil and sediment dermal adherence data has been adopted into the *Exposure Factors Handbook* and Superfund's Part E dermal guidance.

Inhalation Dose-Response Methodologies: Chronic RfC and Exposure-Response Values

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Client Need: EPA Program Offices and Regions, States, other federal agencies, including the Department of Homeland Security, as well as local regulatory authorities are all often confronted with making decisions on acceptable levels of risk from exposures to a large number of pollutants occurring over a wide range of exposure scenarios. Accomplishing this requires having methodologies that can yield health effect reference values that are reliable, defensible and reflective of current science and useful in a variety of real-world situations.

Science Questions: What new science is available to improve the 1994 "Methods for Derivation of Inhalation RfCs and Application of Inhalation Dosimetry" for chronic exposures? What is critical to include in a methodology to evaluate exposure-response relationships for different exposure scenarios to derive the informative health effect reference values?

Approach: NCEA scientists are identifying issues that must be addressed by the methodologies; they will then apply the latest science in their construction and refinement. For the chronic RfC methodology, in-depth critical reviews have been solicited and received from a panel of inhalation toxicology experts for consideration by NCEA scientists. In development of the draft inhalation exposure-response methodology, NCEA experts have developed case-studies (see LTG 1, Poster 11) to identify and address issues related to various exposures scenarios and types of data sets.

Results and Outcomes: NCEA scientists are in the process of synthesizing a broad array of information into practical and valuable methodologies. The chronic RfC panel has suggested overall simplification of the methodology, adoption of existing models for particle dosimetry, incorporation of more recent definitive findings on gas dosimetry and on updating findings on age-related toxicity. In the case of the exposure-response methodology, the results of the case studies have identified important issues to be addressed, which include use of dosimetry, duration extrapolation, consideration of time to recovery for repeated exposures and inclusion of developmental toxicity critical exposure periods. This information is being incorporated into a methodology that will facilitate representation and evaluation of different exposure scenarios with differing types of data sets. The principal outcomes of these two efforts will be methodologies that are relatively simple to apply, reliable, defensible and reflective of current science and useful in a variety of real-world situations.

Impacts: Independently peer-reviewed documents for the Chronic RfC and the Exposure-Response methodologies, both of which were coordinated across federal agencies, will make available new and improved information and methods for acquiring the key information needed to assess risks from inhalation exposures to pollutants. New information sources will include NCEA developed on-line data arrays which will help users rapidly evaluate and apply available toxicology information from a wide-range of sources in risk assessments and decision-making. Clients will have access to consistent, reliable, defensible information reflective of current science.

Advancing the development, evaluation, and use of physiologically-based pharmacokinetic (PBPK) models in risk assessment

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Agency Problem/Client Need: The EPA seeks to develop, evaluate, and, as appropriate, apply physiologically based pharmacokinetic (PBPK) models for internal dosimetry estimation in risk assessments. To succeed, we must educate chemical managers in appropriate ways to review PBPK models and provide them the means to understand the limitations and uncertainties of models that are used in assessments.

Science Questions: What methods and evaluation tools are needed to advance the use of PBPK models in the derivation of scientifically sound and supportable points-of-departure (PODs) for cancer and noncancer dose-response analysis that incorporate what is known about a chemical's toxicokinetics and mode-of-action? For example: How can we best use PBPK models to estimate the human equivalent dose corresponding to a rodent-derived benchmark dose? How can we evaluate the uncertainties in PBPK model estimates? How can we make modeling or insights from modeling more accessible?

Approach: NCEA collaborates with experts throughout EPA and the international community to advance methods and resources for the development, evaluation, and use of PBPK models in risk assessment. Areas of active research include (1) characterization of uncertainty and variability in model structures and parameter values, (2) methods and criteria for evaluating and comparing models, and (3) coupling of PBPK models to other dosimetry and toxicodynamic models. A number of essential information and training resources are also being developed.

Results/Outcomes: NCEA helped organize (and were major contributors to) two recent international workshops, one addressing the challenge of characterizing uncertainty and variability in PBPK models (Barton et al, 2007) and one addressing good practices in PBPK model development and use (publication in progress). Both workshops improved consensus in the international research community on the priority method and data needs and stimulated collaborative efforts to meet those needs. EPA has also taken the lead in developing critical information and training resources on the development and use of PBPK models in risk assessment including a major report (EPA/600/R-05/043F; August 2006), and two peer-reviewed publications on model evaluation (Clark et al., 2005; Chiu et al., 2007). Ongoing development of essential resources include (1) an electronic archive for models that have been or are being used in EPA risk assessments, with the supporting documentation and data needed to conduct a thorough and independent evaluation of the model, (2) databases for critically needed model physiological parameter values, (3) an annotated bibliography of relevant literature, and (4) training materials for risk assessors, e.g., case studies, course presentations.

Impacts: Increasingly, PBPK models are being used to replace default adjustment factors, in extrapolating PODs from experimental animals to humans, and in extrapolating PODs from one route of exposure to another when route-specific dose-response data are not available. NCEA's research and development of information resources directly supports the use of PBPK models in Integrated Risk Information System (IRIS) and other EPA programs including the Office of Pollution Prevention and Toxics (OPPT)'s Hazardous Air Pollutants (HAPs) Test Rule Program; National Homeland Security Research Center (NHSRC)'s Provisional Advisory Levels (PALs) Program; and OPPT's Acute Exposure Guideline Levels (AEGLs) Program (see LTG1 Poster 4). EPA's collaboration with national and international modelers has greatly benefited consensus in these areas of research, and has focused the research community on priority method and data needs, with the result that many of these needs are currently being addressed.

Utilizing early lifestage data in risk assessment

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Agency Problem/Client Need: Legislative mandates and EPA policies state that EPA will consider risks to infants and children consistently and explicitly as part of risk assessments generated during its decision-making process. EPA's regulatory programs and regional risk assessors need appropriate resources for utilizing available early lifestage data to carry out these mandates. Assessments that use only available chemical-specific data are often limited to data from adults and do not necessarily account for the lack of data at other lifestages.

Science Questions: What physiological and behavioral differences exist between children and adults, and how do these differences alter responses to exposure to environmental agents? How can available data be utilized to better predict potential health risks to children?

Approach: To evaluate the potential for adverse health outcomes during early lifestages, there is a need for a multi-faceted approach. In 2006, EPA published *A Framework for Assessing Health Risk of Environmental Exposures to Children* that focuses on understanding underlying biological events (e.g., mode of action), physiological parameters (e.g., ventilation rate), behavior, toxicokinetics, and critical windows of development, encourages evaluation of potential for adverse health outcomes at all developmental lifestages, and addresses integration of adverse health outcomes and exposure information across lifestages. This publication encourages consideration of data on how children have different exposure behaviors, different metabolism, and may have different inherent susceptibilities in future human health risk assessments.

Results/Outcomes: Considering early lifestage data in risk assessment results in a comprehensive and transparent evaluation of data on exposure and response to determine the potential for vulnerability. A number of recent EPA documents address the issues relating to exposure differences across age groups, including *Child-Specific Exposure Factors Handbook* (2002, 2007), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (2005), *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (2005), and *A Framework for Assessing Health Risk of Environmental Exposures to Children* (2006). Other projects underway address differences in metabolism. Through collaboration with the National Center for Computational Toxicology (NCCT), a related database for physiological parameters in developing rodents has recently been made available (http://www.epa.gov/ncct/parameters.html). Products being finalized include a report characterizing early-life differences in classical pharmacokinetic parameters (e.g., half-life) suitable for informing pharmacokinetic adjustments in data-limited situations and a relational database of physiological parameters useful for developing probabilistic or deterministic physiologically based pharmacokinetic (PBPK) models for children.

Impacts: The added value of using early lifestage data to risk assessment is a more comprehensive evaluation of the potential for vulnerability of the population. Specifically, these efforts have provided statistical data on various factors assessing child exposures, on selecting age groups to consider when assessing childhood exposure and potential dose to environmental contaminants, and on potency adjustments for early lifestage exposure to carcinogens with a mutagenic mode of action. Utilizing early lifestage data in risk assessment highlights where existing data are present, as well as where data gaps exist. This facilitates increased transparency related to uncertainties in risk assessment and provides direction for priority research needs. In addition, this has improved risk communication regarding concerns related to early lifestage exposures.

Characterization of environmental risks to older adults

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Agency Problem/Client Need: The growing proportion of older adults has increased the need to understand how age-related changes in physiology, behavior, disease status, or other health conditions may impact exposure and toxic response to environmental agents. Information is needed to better quantify risks and characterize uncertainty to ensure that regulatory decisions are sufficiently protective of potentially susceptible aging populations.

Science Question: How do changes in physiology, behavior, disease status, or other health conditions alter response to environmental agents in older adults?

Approach: NCEA has several efforts underway for improving the state of knowledge regarding age-related changes that may alter susceptibility to the toxic effects of environmental pollutants in older adults. Early efforts focused on examining the body of evidence on the environmental origins of neurodegenerative diseases of older American populations. These early efforts, the vast emerging literature on aging population, and the potential toxic response to environmental agents led to the study of the functional, physiological, and biochemical changes that occur in elderly persons, in addition to the pharmacokinetic factors likely to influence the response to environmental exposures in older adults. More recently, a panel of experts discussed existing exposure data, gaps, and needs; current relevant research on the behavior and physiology of older adults and practical considerations of the utility of an *Exposure Factors Handbook for the Aging* in conducting exposure assessments.

Results/Outcomes: NCEA sponsored and participated in the conference, *"Early Environmental Origins of Neurodegenerative Disease in Later Life: Research and Risk Assessment,"* held in New York City on May 16, 2003, which resulted in a mini-monograph published in *Environmental Health Perspectives* (vol. 113, issue 9, September 2005). In 2006, NCEA published a report entitled *Aging and Toxic Response: Issues Relevant to Risk Assessment,* which provides a broad overview of the age-related toxicokinetic and toxicodynamic impacts of environmental agents. The review of the literature has resulted in the development of a physiological parameters database for the aged and for four disease states of the geriatric population. This database will facilitate physiologically based pharmacokinetic (PBPK) modeling of environmental agents. In the area of exposure assessments, the report from the expert panel meeting held in February 2006 highlighted areas of ongoing research and identified several sources of existing data that may be used to better characterize the activity patterns and behavior of older adults. In addition, recommendations for additional research were made, including evaluating the effect of ethnicity, socioeconomic status, and decreased functionality on the variability of physiological function and activity patterns in older adults.

Impacts: These efforts are improving the state of knowledge regarding environmental exposure, chemical disposition, and toxic response in older adults. Results of these efforts will assist in targeting specific areas where research is needed to better characterize differential exposures of the older adult population to environmental agents. As indicated by recent enquiries concerning the availability of the physiological parameters database, many in the PBPK modeling community (and other fields) are eager to put this resource to use. Summarizing the available exposure and physiological parameters data into an existing *Exposure Factors Handbook for the Aging,* or a separate document, will help assessors better characterize exposure, risk, and uncertainty to older adults.

Use of mode of action information to inform human health risk assessment

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Agency Problem/Client Need: To enhance utilization of the best available scientific information on the modes of action (MOAs) of toxicity of environmental chemicals in human health risk assessments. To foster communication within and outside the Agency with the goal of educating risk assessors about current scientific developments while, in turn, informing research scientists about priority data needs for human health risk assessment.

Science Question: To what extent can MOA data inform decisions on critical issues such as the relevance of high-dose effects to low-level environmental exposures, susceptibility and variability of response within and among species and the quantitative impacts of these considerations on dose-response functions used in human health risk assessment?

Approach: This effort includes four general project areas. The first encompasses general approaches to analyzing and applying MOA information in human health risk assessment. Considered are ways to expand analyses of individual MOAs to the larger context of background processes as well as the associated and independent toxic effects of a chemical (i.e., across multiple MOAs and outcomes). Also addressed are the implications for lifestage susceptibility of a range of cancer MOAs. These include mutagenesis, which is associated with enhanced sensitivity in early life as well as non-mutagenic MOAs. A second project area involves pharmacokinetic and pharmacodynamic analyses to understand such issues as the human relevance of rodent cancers (e.g., mouse lung and liver tumors) and human population variability based on genetic polymorphisms in metabolizing enzymes. While some focus on cancer, other projects are exploring pharmacokinetic and pharmacodynamic modeling of noncancer outcomes such as developmental neurotoxicity. A third area explores dose-response modeling implications of certain MOAs including the key factors determining low-dose linearity/nonlinearity (e.g., additivity to exogenous or endogenous factors). One potential MOA of interest is the generation of reactive oxygen species, which mediate a number of diverse mechanistic effects ranging from DNA damage to lipid peroxidation to stimulation of intracellular signaling. Finally, integrated with these efforts are projects on particular Integrated Risk Information System (IRIS) Program chemicals (e.g., formaldehyde, trichloroethylene). This final project area explores individual MOAs, integrated biologically motivated dose-response models, and human relevance issues.

Results/Outcomes: Overall, the anticipated outcomes include the development of tools leading to the efficient and appropriate use of MOA information in chemical hazard and dose response assessments and accompanying analyses of particular MOAs, toxicity pathways, chemicals, and health effects. Associated outcomes include improved communication with the research community to facilitate identification of data gaps and implementation of research to support sound decisions regarding MOA implications for human health risk assessment.

Impacts: Taken together, the described projects demonstrate the potential for MOA data to inform human health risk assessment approaches. This supports the enhanced use of scientific information in decision-making about key issues such as the relevance of animal data to estimates of human risk and the associated implications for low-dose extrapolation.

Use of biologically-based dose response models

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Agency Problem/Client Need: Various programs, such as the Office of Air and Radiation (OAR), Office of Pollution Prevention and Toxics (OPPT), Office of Water (OW), and Integrated Risk Information System (IRIS) Programs, require the development of biologically based dose-response (BBDR) models and the evaluation of existing models.

Science Questions: Increasing amounts of pharmacodynamic data are now available that inform changes at the tissue level that occur in response to exposure to a xenobiotic. However, while there is some experience in the use of physiologically based pharmacokinetic modeling in risk assessment, the relevance of biologically based dose response (BBDR) modeling has not been demonstrated or discussed adequately at the Agency. What are the potential uses of biologically based models? What are the requirements, uncertainties, and data needs if BBDR models are used for (1) low-dose human risk extrapolation and (2) developing testable hypothesis to understand mechanisms better?

Approach: We present case studies for five chemicals where mechanistic information was available: methyl mercury, ethanol, chlorpyrifos, benomyl, and formaldehyde. For the first four chemicals, a pharmacodynamic dose-response model for mid-brain development was used to quantitatively evaluate critical neurodevelopmental processes and to identify critical windows in these processes where the chemical most impacted early brain development. The model was then extended for early neocortical development. In the case of formaldehyde, a previously published two-stage clonal expansion model for cancer was evaluated for extrapolating results of rodent bioassay data to estimate respiratory tract cancer risk at human exposures. This model incorporates pharmacokinetic and computational fluid dynamics modeling to provide regional dosimetry input to a two-stage cancer model. Such regional dosimetry impacts considerably on interspecies extrapolation in the case of a highly reactive and soluble gas. We carried out extensive sensitivity analyses on uncertainties in parameters, as well as in model specification, and examined to what extent they influenced the prediction of low-dose rodent and human risk.

Results/Outcomes: For the first four chemicals, BBDR modeling provides a useful quantitative approach to test hypotheses about normal neocortical development and chemically induced alterations in neurodevelopment. BBDR modeling also integrates available data, and frames hypotheses regarding the relative role of neurogenesis versus apoptosis in regulating early embryo/fetal brain development, thereby pointing to critical data needs. In the case of the two-stage model for formaldehyde, uncertainty analyses of parameters and model specification showed that maximum likelihood estimates of low-dose risk based upon this model could vary by many orders of magnitude, both for the human and rodent.

Impacts: BBDR models enable integration of toxicodynamic data, can be coupled with toxicokinetic models, and can be valuable tools for hypotheses generation and testing. This poster extends the discussion on uncertainty and variability from another poster (see LTG 2 Poster 6) in this session, and demonstrates that uncertainty and sensitivity analyses are essential tools in BBDR model evaluation. Our analyses demonstrated the extreme sensitivity of two-stage cancer models to underlying parameters such as the division and death rates of initiated cells and the use of control tumor data when used for extrapolation of risk from rodent bioassays to human exposures.

Dose-response modeling at EPA: research and development

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Agency Problem/Client Need: Dose-response modeling currently serves as the basis for toxicity values in most EPA quantitative risk assessments. Several publications in this field indicate that it is a rapidly evolving discipline, and EPA risk assessors need help in identifying and applying valid methods for dose-response modeling. Important questions have arisen with the increased use of benchmark dose (BMD) modeling.

Science Questions: How does one derive a point of departure (POD) that avoids subjectivity and accounts for model uncertainty? How accurate are our estimates of confidence limits (e.g., lower confidence bounds on the benchmark dose [BMDLs])? How can POD values derived for one exposure duration be extrapolated to others? Statistical questions also arise. How should one treat data that may be lognormally distributed? What are appropriate statistical inferences when an optimized parameter estimate reaches an established boundary? How should a POD for the combined risk of multiple tumor sites be estimated?

Approach: *To answer questions on model uncertainty*, NCEA is investigating methods (e.g., BMD model averaging) that weight results based on statistical measures of model fit. NCEA also continues to investigate the use of models uniquely suited to certain situations or data. *To answer questions on estimation of confidence limits*, NCEA is comparing different statistical methods for characterizing response distributions. *To answer questions on the extrapolation of PODs across exposure durations*, NCEA is investigating the use of new categorical regression (CatReg) and time-dependent dose-response software. *NCEA is actively researching statistical methods to resolve issues* such as those related to data with an underlying lognormal distribution, model parameters that hit assigned boundaries, and risk from multiple independent tumor sites. *To improve consistency and scientific credibility of dose-response assessments*, NCEA continuously monitors the concerns of EPA risk assessors with Web site feedback and surveys of literature for methods or tools that can be used or developed to assist them.

Results/Outcomes: NCEA has developed models useful for certain situations, e.g., exponential models (for cholinesterase inhibition data), a dichotomous Hill model (for saturable effects), and background dose additivity models (for effects with significant background incidence). NCEA has enhanced time-dependent ten Berge and CatReg models, increasing their usefulness and accessibility for risk assessors to extrapolate dose-response data across exposure durations and effect severity. Some of the NCEA research reports prepared on the aforementioned statistical issues and others have led to the enhancement of assessments (e.g., methanol and nitrobenzene) through improved software or methods for the evaluation of risk (e.g., from multiple tumor sites). One report theoretically confirmed the asymptotic distribution that EPA currently uses to estimate lower confidence limits when optimized parameter values reach established bounds and outlined a general multiparameter framework for such situations.

Impacts: EPA dose-response methods are being used by thousands of risk assessors throughout the world, so the associated software tools and training materials must be maintained to be current and effective. Keeping up with the state of the science for dose-response assessments and the needs of risk assessors will allow EPA to produce defensible assessments and encourage research in areas where uncertainties are large.

Whole mixture methods for assessing health risks from exposures to chemical mixtures

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Agency Problem/Client Need: The Safe Drinking Water Act Amendments (1996), Food Quality Protection Act (1996), and Comprehensive Environmental Response, Compensation, and Liability Act (1980) mandate that EPA assess human health risks posed by complex mixtures. Complex mixtures can consist of hundreds of environmental contaminants (e.g., drinking water disinfection by-products [DBPs], polycyclic aromatic hydrocarbons [PAHs], total petroleum hydrocarbons [TPHs]). Quantitative risk assessment methods that consider chemical composition and environmental exposures along with toxicity information are needed to characterize human health risks. Variations in chemical composition that can change the relationship between mixture dose and response make health risk assessment of complex mixtures challenging.

Science Questions: Can whole mixtures be assessed when a large fraction of the chemical composition is unidentified? Can we find ways to test whole mixtures and extrapolate the results to assess health risks from exposures to similar mixtures? Can we better characterize epidemiological exposures to complex mixtures and improve population health risk measures?

Approach: EPA (2000) provides whole mixture risk assessment methods, developed to (1) use toxicity data directly from a toxicological or epidemiological evaluation of an environmental mixture (or its concentrate), (2) use surrogate information on a sufficiently similar mixture to evaluate the mixture of concern, or (3) evaluate the whole mixture using chemical and toxicological evaluations of its fractions.

Results/Outcomes: NCEA provides statistical analyses and develops mixture risk assessment methods to evaluate developmental effects in rodents exposed to DBP mixture concentrates, accounting for the toxicity of a large unidentified chemical fraction. NCEA also conducts epidemiological research to improve DBP exposure estimates and investigate developmental effects. These efforts provide whole mixture toxicity and exposure data, useful in developing reference values (RfV) and methods for assessing complex chemical mixtures. The Office of Water may use these studies to determine how well existing regulations protect human health. An RfV for a whole mixture can be used as a surrogate to assess a related mixture, thus applying the concept of “sufficient similarity”. Developing criteria for determining similarity for DBP mixtures and for PAH mixtures will allow the assessment of environmental mixtures using data on a similar well-studied mixture; thereby avoiding resource-intensive studies on environmental complex mixtures while ensuring health protection. If the mixture of concern consists of chemically and toxicologically well-characterized fractions, then its risk can be assessed on the risks of the individual fractions. EPA is assessing the use of TPH fractions to estimate risks posed by TPH mixtures. Whole mixture methods for DBP, PAH and TPH will improve EPA’s assessments of drinking water, combustor emissions, and contaminated sites.

Impacts: The development of new methods and RfVs by NCEA and our collaborators for assessing the risks associated with exposures to complex mixtures and reductions in the uncertainties associated with these methods are essential to EPA. Such advancements in risk assessment improve the credibility of risk characterizations and generate improved risk information from limited resources.

Component-based health risk assessment methods for chemical mixtures

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Agency Problem/Client: Need: Legal mandates (e.g., Food Quality Protection Act ,1996; Comprehensive Environmental Response, Compensation, and Liability Act [CERCLA], 1980) and community concerns obligate EPA's Program Offices and Regions to address risks posed by exposures to environmental chemical mixtures, e.g., dioxins, polycyclic aromatic hydrocarbons (PAHs), polybrominated diphenyl ethers (PBDEs), drinking water disinfection by-products (DBPs), organotins (OTs), pesticides. Because application of component methods, which evaluate mixture risk based on data developed for individual mixture components, is practical and their interpretation is straightforward, these methods are routinely used in setting regulations (e.g., emissions regulations) and developing site remediation strategies.

Science Question: Because of the continued use of component methods, assessments of environmental mixtures are often complicated by differential population sensitivities, differential and multiple route exposures, and by toxicological interactions. How can we best continue ongoing development and improvement of risk assessment methods to quantify human exposures and determine health risks, including examinations of their scientific credibility and quantitative uncertainty?

Approach: NCEA has both developed and applied component-based methods and guidance for assessing chemical mixtures health risks for use by Agency risk assessors in the Program Offices and Regions. Exposure methods have evolved through independent mixtures assessments conducted by NCEA and include simulated multiple-route exposures based on pollutant concentrations in contaminated media, statistical distributions of human exposure factors and measurements of pollutant concentrations in human tissues.

Results/Outcomes: The following NCEA efforts enhanced the accuracy of assessments of risks posed by chemical mixtures: (1) Relative Potency Factors (RPFs) for PAH and for pesticide mixtures; (2) improved design of mixtures toxicity experiments; (3) use of mode of action (MOA) data for DBPs and OTs; (4) exposure assessments for dioxins, PBDEs, DBPs and OTs; and (5) integration of mixtures exposure and risk assessment methods into cumulative risk assessments. Updating PAH RPFs will improve assessments of combustion facility emissions risks. Assessment of uncertainty in RPF applications to pesticides has improved risk characterization. Experimental design improvements enhance the efficiency of mixtures assays. A DBP approach utilizing MOA data can be generalized to other multi-route mixtures exposures. Research has demonstrated that deposition of gas-phase dioxins to terrestrial vegetation is the primary human exposure pathway, showed that kinetic models could link human exposures and body burdens, and resulted in the Dioxin Sources Inventory. Human exposure method applications have showed that PBDE exposures likely result from house dust and suggest that low-level OTs exposures can result from leaching from PVC pipes. New mixture/cumulative risk methods are available for future assessments.

Impacts: EPA program offices and regions use component-based methods and exposure information developed or improved by NCEA to regulate mixtures. EPA used a mixtures approach for setting haloacetic acid levels in the M/DPP Stage 2 Drinking Water Rule to protect public health, and Site Managers are directed by the Risk Assessment Guidelines for Superfund (RAGS) to use response addition, a component approach, to support cleanup-level decisions at Superfund sites.

Evaluation of uncertainty, data derived uncertainty factors, and variability

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Agency Problem/Client Need: There is strong interest in further formal, quantitative, analysis of uncertainty and variability in risk assessments; in moving toward using chemical-specific data to derive data-driven uncertainty factors; in capturing the full range of uncertainties in estimating expected values; in estimating confidence limits on risk; and in quantitatively characterizing population variability.

Science Questions: Can we develop a sound, standardized approach to developing data-derived (non-default) values for inter- and intraspecies extrapolation in noncancer risk assessment? Can we quantitatively characterize uncertainty and variability to provide well-defined central estimates and confidence limits around risk estimates?

Approach: Several efforts are underway to increase objectivity, consistency, transparency, and confidence in how uncertainty is addressed in Agency risk assessments. First, key sources of uncertainty are being defined and clarified in a set of white papers, including statistical and dose-response modeling, cancer risk assessment, mode of action identification, and integration of data from multiple levels of biological organization. Second, application of Markov Chain Monte Carlo (MCMC) methods to derive a probability distribution of cancer risk is being developed. Third, an analysis of human variability in key physiological determinants of internal exposure is also in progress, including demonstration of their impact on dosimetry among humans. Fourth, approaches to quantify uncertainty in human equivalent concentrations or doses estimated via physiologically based pharmacokinetic (PBPK) models are being explored. Fifth, guidance for the replacement of default values for inter- and intraspecies uncertainty factors is being developed. We also expect to explore other ways to formally characterize uncertainty and variability.

Results/Outcomes: The white papers stimulated deliberations on methods to characterize uncertainty in cancer risk estimates and provide background information for the National Academies of Sciences for cancer risk assessment. The probability MCMC-derived distribution of risk contributes important information for the quantitative evaluation of uncertainty. Reports on the rationale for characterizing human interindividual physiological and biochemical variability and on alterations in dosimetry that occur because of disease status have been developed. NCEA provided the leadership to the Risk Assessment Forum in developing guidance on allometric scaling for interspecies extrapolation and on developing data-derived uncertainty factors for both inter- and intraspecies extrapolation. Characterization of risks associated with tetrachloroethylene exposure, as an example analysis, includes quantification of risks in all affected tissues, not just the critical target organ. Information from uncertainty and variability analyses has lead to identification of critical data gaps and prioritization of research needs.

Impacts: We intend to develop tools that will improve the ability of risk assessors to formally and soundly characterize and present the key uncertainties in chemical risk assessment. We intend to estimate the distribution of cancer risk to support decision-making and cost/benefit analysis. We will characterize human interindividual variability to both provide values that would protect susceptible populations and to help identify susceptible subpopulations and characterize their risks.

Approaches to Address Emerging Issues in Risk Assessment

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Agency Problem: Powerful new technologies (e.g., genomics) and new issues (e.g., nanotechnology) have emerged that impact risk assessment practices across all EPA programs and regional offices. As a result, NCEA must adapt its risk assessment methodologies, and EPA needs Agency-wide strategies to address these challenges.

Science Question(s): What approaches and activities are needed to utilize genomics data in risk assessment; to develop methods for microbial risk assessment; to understand the issues in nanotechnology risk assessment; and to advance risk assessment practices for chemicals lacking toxicity data?

Approach: NCEA is recognized within and outside the Agency as a leader in human health risk assessment. NCEA scientists respond to emerging issues in risk assessment by developing new approaches, methods, and guidance. To pursue these avenues, NCEA has formed partnerships to collaborate within and outside the Agency. NCEA scientists contribute as members of EPA workgroups and projects, and by publishing articles and documents.

Results and Outcomes: NCEA is involved in numerous projects to develop risk assessment approaches (e.g., tools, guidance) to address emerging issues. This poster highlights NCEA's work, in collaboration with others within and outside of EPA, to meet four of these challenges:

- Microbial Risk Assessment: NCEA is developing modeling options for pathogen-induced illness in humans, particularly with respect to variability and uncertainty in a sparse data environment. NCEA has produced two reports and several journal articles addressing key microbial risk assessment issues.
- Genomics: NCEA scientists identified issues for the use of genomics in risk assessment (2003); participated in the SPC's Genomics Task Force white paper and guidance development; co-chaired the RAF Genomics Training Technical Panel that implemented the training (2007) recommended by the SPC; and leads the NCCT-funded project to develop an approach and case study for using toxicogenomics data in risk assessment.
- Nanotechnology: NCEA scientists contributed to the EPA's Science Policy Council (SPC) Nanotechnology white paper (2007); lead the nanomaterial case studies recommended by the white paper; provide support to the Office of Pesticides Prevention and Toxic Substances (OPPTS); participate in the development of the ORD Nanomaterial Research Strategy; and have published articles on the risk assessment of nanomaterials
- Predictive Modeling Approaches: NCEA is evaluating and developing modeling approaches for identifying potential toxicity endpoints, surrogate chemical selections, or estimations of toxicity values for use in EPA assessments for chemicals with unknown or limited toxicity information. NCEA collaborates with other ORD programs, laboratories and centers to use predictive approaches (e.g., Oncologic from OPPT) and refine databases (e.g., dssTOX & ToxCast from NCCT).

Impacts: NCEA has been responsive to emerging issues in human health risk assessment through the development and testing of new risk assessment methodologies. Further, involvement in Agency-wide efforts to address these issues has led to the identification of key issues, considerations, data gaps, and research needs. These activities have a significant impact on risk assessment at EPA programs including IRIS, OPPTS, OSWER, OAR, and OW.

Leadership, Collaboration, and Promotion in the Development and Use of Risk Assessment Models, Methods, Databases, and Guidance

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Agency Problem: U.S. Environmental Protection Agency (EPA) Program Offices, EPA Regions, States, local regulatory authorities, and other stakeholders need state-of-the-science human health risk assessment methods, models, and databases to tackle complex science-based questions in the processes of risk assessment. The Human Health Risk Assessment (HHRA) program plays a leadership role in the development of risk assessment models, methods, databases, and guidance documents. Collaboration and promotion of these tools through training, publications, and other outreach efforts serves to incorporate these approaches into risk assessment practice within and outside the Agency.

Challenges: How does HHRA demonstrate its leadership in addressing significant cross-Agency risk assessment issues? How can HHRA best collaborate, promote, and communicate the use of the state-of-the-science methodologies into the practice of human health risk assessment within NCEA, ORD, EPA, and the risk assessment community nationally and internationally?

Approach: The HHRA program actively identifies major issues in risk assessment, and organizes, participates, and leads teams of experts and utilizes expertise and experience of scientists as well as experts from within and outside the Agency to promote consensus on cross-cutting risk assessment issues faced by the Agency. Working Groups and Technical Panels develop state-of-the-science methods, models, databases, and guidance. Tools developed under the HHRA program are promoted both inside and outside the Agency through training and website access. Stakeholder input and review by scientists from within and outside the Agency is incorporated into the projects, as well as peer-review by independent experts and public comment where appropriate. HHRA continues to revise, update, and provide supplements to the risk assessment tools as advances in scientific understanding allow improvement to specific methods.

Results and Outcomes: The HHRA program has played a leadership role in the development of EPA's risk assessment methods, models, databases, and guidelines that are the premier source of information for the decision-making process for risk assessors and risk managers from EPA Program Offices, EPA Regions, states, and local regulatory authorities. Interaction with scientists both within and outside of the Agency allows the HHRA program to collaborate and promote their state-of-the-science human health risk assessment methods, models, databases, and guidance. Collaboration with various partners augments the expertise within the HHRA program and maximizes available resources. Promotion of these approaches to various stakeholders allows for timely incorporation of these scientific advances into risk assessment practice.

Impacts: The HHRA program's risk assessment methods, models, databases, and guidelines are critical to IRIS Health Assessments, PPRTVs, and Integrated Science Assessments developed within the HHRA program: the are also used extensively to inform human health and risk management decisions by EPA Program Offices and Regions in their risk assessment decisions; and serve as a model for other national and international government entities, resulting in a more consistent and scientifically sound application to human health risk assessment.